UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: September 6, 2019

SUBJECT: **Ethoxyquin**: Summary of Hazard and Science Policy Council (HASPOC) Meeting on July 25, 2019: Recommendations on the Need for Developmental, Reproduction, and Chronic/Carcinogenicity Studies.

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40 CFR: N/A

FROM: Ruthanne Louden, Executive Secretary
HASPOC
Health Effects Division (7509P)

THROUGH: Evisabel Craig, Ph.D., DABT, Co-Chair
Brian Van Deusen, Co-Chair
HASPOC
Health Effects Division (7509P)

TO: Austin Wray, Toxicologist
Kristin Rickard, Acting Branch Chief
Risk Assessment Branch IV (RABIV)
Health Effects Division (7509P)

MEETING ATTENDEES:

HASPOC Members: Elizabeth Mendez, Jonathan Chen, Matt Crowley, Michael Metzger, Kristin Rickard, Anwar Dunbar, Kelly Lowe, Greg Akerman, Evisabel Craig*, Brian Van Deusen*
*Co-chair

Presenter: Austin Wray (Toxicologist)

Other Attendees: Melinda Wilson, Rick Fehir, Ruthanne Louden**, Janet Camp**
**Secretary

I. PURPOSE OF MEETING

A registration review human health risk assessment is currently being prepared for ethoxyquin. The toxicology database for ethoxyquin is complete except for the non-rodent developmental, 2-generation reproduction, chronic/carcinogenicity, immunotoxicity, and neurotoxicity battery studies that are required in accordance with the current 40 CFR Part 158.500 Toxicology Data Requirements. The Hazard and Science Policy Council (HASPOC) previously evaluated the requirements for these studies on August 21, 2014 and recommended the reproduction/fertility, developmental, chronic/carcinogenicity, immunotoxicity, and neurotoxicity battery study requirements be waived (TXR 0053945, J. Leshin, 08/21/2014). At that meeting the HASPOC also recommended that a dermal penetration study and subchronic inhalation study be required. The registrant has submitted those studies and they are incorporated into the Registration Review risk assessment. Since the time of the last HASPOC meeting the literature studies that informed the HASPOC decision on the developmental and reproduction study requirements were re-evaluated and found to be unacceptable based on the 2012 HED literature review guidance. Furthermore, the approach used previously to estimate cancer risk in the absence of guideline carcinogenicity studies is not consistent with current practice, thus the requirement for a chronic/cancer study needs to be re-examined. The HASPOC met again on July 25, 2019 to determine if required developmental, reproduction, and chronic/carcinogenicity studies are necessary to support the registration review risk assessment for ethoxyquin.

II. SUMMARY OF USE PROFILE, EXPOSURE, AND HAZARD CONSIDERATIONS

a. Use and Exposure Profile

Ethoxyquin (1,2-dihydro-6-ethoxy-2,2,4-trimethylquinolene) is an antioxidant currently registered for use as a deterrent of scald in pears through post-harvest (indoor) application via a drench/in-line spray treatment, thermal fogging and/or impregnated wraps. Currently eight conventional products are registered: two emulsifiable concentrates, one soluble concentrate and five impregnated materials. The technical product is 99% active ingredient (a.i.) and end use products range from 0.1 to 46% a.i. The maximum application rates vary by treatment method; 2,700 parts per million (ppm) for drench/in-line spray treatment (i.e., 0.022 pounds active ingredient [ai] per gallon solution), 1.07×10^{-5} pounds ai/pound of fruit for thermal fogging, and 1,000 ppm per piece for impregnated paper wraps. Ethoxyquin is also used for preservation of

color in the production of chili powder, paprika, and ground chili and as a preservative in animal feed with food additive tolerances established by the Food and Drug Administration in/on the specified spices, as well as, meat, poultry and eggs.

Ethoxyquin is currently undergoing registration review. Dietary (food only), and occupational handler (short- and intermediate-term dermal and inhalation) and post-application exposures (sorters and packers; short- and intermediate-term dermal and inhalation) are anticipated based on the use patterns of ethoxyquin products with active registrations. PPE on registered labels requires handlers, packers, sorters, and persons otherwise handling treated pear or impregnated paper wraps to wear baseline attire (i.e., long sleeved shirt, long pants, and shoes plus socks) and chemical-resistant gloves. Not all labels currently require the use of PPE. Adequate label restrictions regarding wash-water recycling practices are anticipated to prevent ethoxyquin from reaching drinking water sources. There are no ethoxyquin products registered for residential use and no products registered for application to residential areas. Off-site transport (i.e. spray drift) during occupational application is not anticipated based on the use pattern.

b. Toxicity Profile

Ethoxyquin is an antioxidant that is used to deter scald in pears after harvesting and as a preservative in animal feed and spices. Its ability to induce drug metabolizing enzymes and modify the carcinogenic properties of known carcinogens in mammals is well studied in the literature; however, a toxic mammalian mode of action for ethoxyquin is not established.
The primary target tissues of ethoxyquin following oral exposure varied across mammalian species. Dogs were the most sensitive species examined and exhibited effects primarily in the liver. Liver toxicity – elevated liver enzymes [alkaline phosphatase (ALP) and alanine aminotransferase (ALT)], depletion of hepatocellular glycogen, and bile stasis – was evident without signs of morbidity following acute exposure to 200 mg/kg and progressed with repeated dosing. A reduction in white blood cell count was also observed alongside hepatocellular glycogen depletion following acute exposure. Dogs appeared moribund (body weight loss and myriad agonal clinical signs) within 5-21 days following repeated exposure to oral doses $\geq$100 mg/kg/day and exhibited a more diverse series of liver effects including elevated enzyme levels [gamma glutamyltransferase (GGT) and aspartate aminotransferase (AST) alongside ALP and ALT], increased bilirubin, dark livers, cytoplasmic vacuolation, hepatocellular necrosis, porphyrin-class pigment in the liver, and bile duct hyperplasia at dose levels 10x lower than the acute liver effects. Decreased body weight was observed alongside liver effects following repeated capsule dosing and was accompanied by reduced food consumption. No sex-related differences were observed.

Liver toxicity, body weight decrements, and mortality were also common observations in rats; however, they were noted at dose levels 6-20x above those eliciting similar effects in dogs. Acute oral exposure was moderately toxic to rats (Category III). Mortality was observed in rats within 2-4 days of the initial dose in both acute and repeat dose studies and was preceded by a series of agonal clinical signs at dose levels $\geq$600 mg/kg. Deceased rats exhibited gastrointestinal, kidney, and liver lesions, evidence of hemorrhage in thymus, red fluid in lungs and bladder, matting around eyes, nose, mouth, urogenital area, and anogenital area. Although the liver was the target tissue in both rats and dogs, the manifestation of toxicity was not

identical across species. Liver enzyme levels were elevated in rats but were also accompanied by other unique clinical chemistry changes (decreased glucose levels and increased cholesterol levels) indicative of liver toxicity as well as increases in liver weight and hepatocellular swelling. In addition to a distinct response in the liver, ethoxyquin toxicity in rats was more pervasive. Repeat oral dosing for 90 days to doses ≥200 mg/kg/day elicited a multitude of clinical chemistry changes related to kidney function (increased ions, blood urea nitrogen, and protein levels) alongside microscopic changes in kidneys (tubular dilation, tubular epithelium regeneration, papillary necrosis, hyaline droplets, and nephropathy) and, at the same dose levels, perturbations of the thyroid hormone homeostasis concurrent with thyroid enlargement, anemia, and a decrease in white blood cell count. Papillary necrosis and acceleration of chronic nephropathy in rats was also reported in the open literature at comparable (250 mg/kg/day: Neal et al. 2003; Manson et al. 1992) and lower dose levels (~66 mg/kg/day; Hard and Neal 1992) from dietary exposure ranging from 3 to 18 months. An increased incidence of urothelial hyperplasia, pyelonephritis, and eosinophilic cytoplasmic inclusions and protein accumulation in the cortex were also noted in rats following prolonged exposure to 250 mg/kg/day in the diet (Hard and Neal 1992; Manson et al. 1992; Manson et al. 1987). Furthermore, studies from the open literature indicated that males exhibited more severe kidney toxicity compared to females when exposed to comparable doses in the diet (Neal et al. 2003; Hard and Neal 1992; Manson et al. 1992). Toxicity in the kidneys and thyroid manifest at doses 2-6x lower than the adverse liver effects indicating these tissues were more sensitive to ethoxyquin exposure in rats. Though more sensitive than the liver effects, the kidney, thyroid, and hematology effects in rats were still observed at dose levels 3-10x above the adverse effects in dogs indicating lower sensitivity in this species.

No evidence of increased prenatal susceptibility was reported in the guideline rat developmental toxicity studies, the range-finding rat and rabbit developmental studies funded by NTP, or the open literature. Pregnant rats orally exposed to a 98.2 % technical ethoxyquin formulation at dose levels up to 350 mg/kg/day exhibited slight changes in body weight gain without an adverse impact on body weight and no indication of compromised fetal health. Similarly, no evidence of maternal or developmental toxicity was observed in rats orally exposed to a 67% ethoxyquin formulation up to 500 mg formulation/kg/day (~335 mg ai/kg/day; Kheral et al. 1979). The range-finding rat developmental study funded by NTP reported clinical signs of toxicity (sedate, rough hair coat, and blue urine and feces) in rat dams at 400 mg/kg/day progressing to more severe clinical signs and mortality at higher dose levels. Consistent with the other studies, there was no evidence of developmental toxicity in the NTP range-finding rat developmental study. The range-finding rabbit developmental study funded by NTP reported clinical signs of toxicity and decreased body weight, late abortions (between gestation day 17-24), total resorptions, and mortality in rabbit does at or above 200 mg/kg/day. The abortions and total resorptions were also considered evidence of developmental toxicity given the etiology of these effects are not known. Doe mortalities that potentially reflected a response to acute exposure were observed at doses ≥600 mg/kg/day based on deaths that occurred within 2 days of the first exposure. Guideline studies reporting on postnatal toxicity in mammalian models were not available and no acceptable studies were found in the open literature. No evidence of toxicity in immune or nervous system tissues was observed in the guideline studies or the open literature. Several of the clinical signs noted in moribund animals (ataxia, hypothermia, and hypoactivity) from the

guideline studies could be indicative of neurotoxicity but are more likely an agonal response to excessive exposure.

Ethoxyquin was moderately toxic following acute dermal exposure (Category III) and slightly irritating to the skin (Category IV). It was identified as a weak dermal sensitizer in animals; however, contact dermatitis is frequently observed in humans that interact with the chemical in occupational settings. There were no repeat dose dermal studies to characterize the response to prolonged dermal exposure. Ethoxyquin was also moderately toxic following acute inhalation exposure (Category III) and was not an ocular irritant. Repeated inhalation exposure up to 1 mg/L did not elicit adverse systemic or portal of entry toxicity in rats.

III. STUDY WAIVER REQUESTS

a. Non-rodent Developmental Toxicity

1. Evidence for developmental toxicity in the ethoxyquin database, open literature and unpublished NTP studies:

Previous risk assessments relied on information from the open literature to evaluate developmental toxicity in non-rodents. These studies (DeSesso and Goeringer 1990[1]; Isenstein 1970[2]) were re-evaluated for Registration Review and determined to be unacceptable based on the 2012 OPP literature guidance. Since the time of that decision, two unpublished developmental range-finding studies conducted by NTP were shared with the Agency.

No evidence of increased prenatal susceptibility was reported in the guideline rat developmental toxicity studies, the range-finding rat and rabbit developmental studies funded by NTP, or the open literature. Pregnant rats orally exposed to a 98.2 % technical ethoxyquin formulation at dose levels up to 350 mg/kg/day exhibited slight changes in body weight gain without an adverse impact on body weight and no indication of compromised fetal health. Similarly, no evidence of maternal or developmental toxicity was observed in rats orally exposed to a 67% ethoxyquin formulation up to 500 mg formulation/kg/day (~335 mg a.i./kg/day; Khera et al. 1979[3]). A range-finding rat developmental study funded by NTP reported clinical signs of toxicity (sedate, rough hair coat, and blue urine and feces) in rat dams at 400 mg/kg/day progressing to more severe clinical signs and mortality at higher dose levels. Consistent with the other studies, there was no evidence of developmental toxicity in the unpublished NTP rat developmental study. The range-finding rabbit developmental study funded by NTP reported clinical signs of toxicity and decreased body weight, late abortions (between gestation day 17-24), total resorptions, and mortality in rabbit does at or above 200 mg/kg/day. The abortions and total resorptions were also considered evidence of developmental toxicity given the etiology of these effects are not known.

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[1] DeSesso J M and Goeringer GC. 1990. Ethoxyquin and nordihydroguaiaretic acid reduce hydroxyurea developmental toxicity. *Reproductive Toxicology*. 4(4): 267-275.

[2] Isenstein RS. 1970. Ethoxyquin in rabbit feed: study of relationship to abortion and early neonatal death. *Am J Vet Res*. 31:907-909.

[3] Khera KS, Whalen C, Trivett G and Angers G. 1979. Teratologic assessment of maleic hydrazide and daminozide, and formulations of ethoxyquin, thiabendazole and naled in rats. *J Environ. Sci. Health B*. 14(6): 563-577.

Doe mortalities that potentially reflected a response to acute exposure were observed at doses ≥600 mg/kg/day based on deaths that occurred within 2 days of the first exposure.

2. **Evidence for developmental toxicity in the toxicology database of similar chemicals:**

Twenty-eight chemicals with ≥80% structural similarity to ethoxyquin were identified using EPA's CompTox Chemical Dashboard; however, no mammalian toxicity data were available for these chemicals. In addition, previous reviews of ethoxyquin including the 2004 Reregistration Eligibility Decision identified quindoxin and flectol H as structurally similar chemicals. After further review, quindoxin is not considered structurally similar and flectol H, while similar in structure and ADME, is not toxicologically similar and thus is not relevant for predicting ethoxyquin toxicity. Consequently, no development toxicity data were available from relevant structural analogs.

3. **Risk assessment considerations:**

The current points of departure (PODs) are based on acute and subchronic oral toxicity studies in dogs. An oral NOAEL from the subchronic dog study with an 8% dermal absorption factor (DAF) was used for the dermal assessment because no route specific study was available. The NOAEL from the subchronic dog study was also used for the inhalation POD. Initially, an inhalation POD was not selected for risk assessment; however, it was determined that due to the limited information on offspring and reproductive toxicity, an inhalation POD and inhalation assessment were necessary to account for the possibility that ethoxyquin can elicit these effects. The level of concern (LOC) and population adjusted dose (PAD) were calculated based on a combination of uncertainty factors for interspecies extrapolation (10X) and intraspecies variation (10X), and, for dietary scenarios, the FQPA SF (1X).

Risk estimates for dietary and occupational exposures based on the current PODs are presented in Appendices A.2 and A.3. There are no dietary (Table A.2.1) risks of concern at the current PODs. The acute dietary risk is 2.8% of the acute PAD and the chronic dietary risk is 21% of the chronic PAD. The LOC for occupational scenarios is 100. There are no occupational risks of concern for combined dermal and inhalation exposure at the current PODs and, for one scenario, with additional PPE (Tables A.3.1-A.3.4). MOEs for occupational handlers using a thermal fogger and post-application scenarios are ≥7,100 and are not of concern. Mixer/loader using an automated system is not of concern (MOE=180) with baseline attire plus gloves whereas mixing, loading, and applying for treatment via mechanically pressurized handgun equipment is not of concern (MOE=120) with addition of double layer clothing.

It is not expected that a guideline non-rodent developmental toxicity study would contribute meaningful information to the risk assessment. Toxicity in the rabbit does was observed at dose levels 2x lower than rats indicating they are more sensitive to exposure compared to rats based on the NTP funded range-finding developmental studies. Despite this additional species sensitivity, it is unlikely a rabbit study would provide a lower POD given that the potentially acute and repeat dose effects observed in the NTP rabbit study occurred at dose levels 3-10x above those eliciting effects in the dog and 6-50x above the current PODs. Furthermore, it is unlikely that a rabbit developmental study would report unique developmental toxicity

information or evidence of increased prenatal sensitivity based on the results of the range-finding NTP study.

Based on a WOE approach, considering all the available ethoxyquin hazard and exposure data, the HASPOC recommends that a non-rodent developmental study be waived at this time. This approach included the following considerations: (1) no evidence of susceptibility in the rat developmental studies in the ethoxyquin database and open literature, and the rat and rabbit range-finding developmental studies funded by NTP; (2) the dog is the most sensitive species whereas the non-rodent developmental study is routinely conducted with rabbits; and (3) a non-rodent developmental study conducted with rabbits is not likely to provide unique developmental information or a lower point of departure.

b. 2-generation Reproduction Study

1. Evidence for offspring and reproductive toxicity in the ethoxyquin database and open literature:

No studies were available in the ethoxyquin database that specifically address offspring and reproductive toxicity across multiple generations in any species. There was no evidence of toxicity in reproductive organs in other guideline studies; however, none of these studies were designed to assess every reproductive parameter examined in the guideline 2-generation reproduction study.

Previous risk assessments relied on information from the open literature to evaluate reproductive and offspring toxicity. These studies (Delaney et al. 1995[4]; Gillman and Voss 1995[5]) were not available to the ethoxyquin team to evaluate the quality and acceptability based on the 2012 OPP literature guidance. The results of the Delaney et al. (1995) are provided in abstract form and are based on a conference presentation. The abstract indicated that offspring toxicity (decreased live pups/litter, decreased pup body weight) occurred at doses (300 mg/kg/day) much higher than doses causing maternal toxicity (increased liver and kidney weights, 75 mg/kg/day) in rats. The Gillman and Voss (1995) study was summarized in the JMPR monograph and by the European Chemicals Agency (ECHA)[6] but the ethoxyquin team was unable to locate the original study. Based on the summary, the study demonstrated that offspring toxicity occurred at the same dose levels that elicited parental toxicity (2.5 mg/kg/day) and that ethoxyquin does not elicit reproductive toxicity up to 5.6 mg/kg/day. These studies suggest offspring and reproductive toxicity are not more sensitive endpoints compared to parental toxicity, but the quality of the studies and the findings could not be independently verified by HED and thus they could not be used for risk assessment.

2. Evidence for offspring and reproductive toxicity in the toxicology database of similar chemicals:

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[4] Delaney JC, Wolfe GW, Jamieson HM, and Chapin RE. 1995. Reproductive effects of ethoxyquin in S-D rats assessed by a continuous breeding protocol. Toxicologist. 15(1):165

[5] Gilman MR and Voss WR. 1995. Reproduction/chronic toxicology study of ethoxyquin with beagle dogs. Unpublished report HRP-MI #203-1.1 from HRP Inc for Monsanto, St Louis, Missouri, USA. Submitted to WHO by the Oregon, Washington and California Pear Association.

[6] https://echa.europa.eu/registration-dossier/-/registered-dossier/19351/7/9/1

Twenty-eight chemicals with ≥80% structural similarity to ethoxyquin were identified using EPA's CompTox Chemical Dashboard; however, no mammalian toxicity data were available for these chemicals. In addition, previous reviews of ethoxyquin including the 2004 Reregistration Eligibility Decision identified quindoxin and flectol H as structurally similar chemicals. After further review, quindoxin is not considered structurally similar and flectol H, while similar in structure and ADME, is not toxicologically similar and thus is not relevant for predicting ethoxyquin toxicity. Consequently, no offspring or reproductive toxicity data were available from relevant structural analogs.

3. Risk assessment considerations:

Risk estimates for dietary and occupational exposures based on the current POD are presented in Appendices A.2 and A.3. The same considerations discussed for the non-rodent developmental study waiver above apply here, except that the open literature contains less verifiable information on postnatal and reproductive toxicity than for prenatal toxicity. Traditionally, offspring and reproductive toxicity considerations in human health risk assessment are informed by data reported in the guideline multigeneration reproduction study in rats. Although a rodent multigeneration reproduction study is not likely to report parental effects at a lower dose than the current PODs given the differences in sensitivity between adult rats and dogs, the available data do not rule out the possibility of postnatal or reproductive toxicity in rats occuring at doses lower than the parental rat effects. Despite this uncertainty, the enhanced sensitivity of the dog to ethoxyquin will likely provide adequate protection in the current PODs to account for the potential offspring and reproductive effects that would be reported in the 2-generation rat reproduction study. This conclusion is based on the following considerations. The lowest dose that elicited toxicity in adult rats following subchronic exposure was 40 mg/kg/day. The effects at this dose level –10% decrease in body weight – are considered equivocal evidence of an adverse response to treatment, but the endpoints for this study were not updated given that they did not impact our current PODs. Assuming that parental effects would occur at a similar dose in the 2-generation reproduction study, the offspring and reproductive effects would have to be at least 10x more sensitive than the adult effects to be below the NOAEL from the subchronic dog study. Given the equivocal evidence of adversity at 40 mg/kg/day in the adult rats, the 10x gap between adult rat toxicity and the current PODs is likely a conservative estimate and could be much larger. As a result, it is anticipated that the PODs based on the subchronic dog study would be protective of the potential for increased postnatal sensitivity and reproductive effects that could be observed in a 2-generation reproduction study in rats. The sensitivity difference between species is not as large for acute exposure (i.e. the dog acute NOAEL is 6X lower than the most conservative rat acute LOAEL); however, a 2-generation rat reproduction study is not likely to report postnatal and reproductive- specific effects (e.g. effects that are not also observed in the parental population) that could be attributed to a single dose exposure and be used as the acute POD.

Rather than requiring a 2-generation reproduction study in the less sensitive species, the dog studies can be used as the PODs for all repeat-dose scenarios including inhalation to be protective of the potential for increased sensitivity in offspring or reproductive effects. There are no dietary (Table A.2.1) risks of concern at the current PODs based on the dog studies. The acute

dietary risk is 2.8% of the acute PAD and the chronic dietary risk is 21% of the chronic PAD. The LOC for occupational scenarios is 100. There are no occupational (Tables A.3.1-A.3.4) risks of concern at the current PODs based on the dog studies at label-required PPE and, for one scenario, with additional PPE. MOEs for occupational handlers using a thermal fogger and post-application scenarios are ≥7,100 and are not of concern. Mixer/loader using an automated system is not of concern (MOE=180) with baseline attire plus gloves whereas mixing, loading, and applying for treatment via mechanically pressurized handgun equipment is not of concern (MOE=120) with addition of double layer clothing.

Based on a WOE approach, considering all the available ethoxyquin hazard and exposure data, the HASPOC recommends that a 2-generation reproduction study in rats be waived at this time. This approach included the following considerations: (1) the rat offspring would have to be 6-10x more sensitive than the adults to exhibit effects at a dose similar to or lower than the PODs currently selected for all scenarios; (2) the body weight effects observed at the most conservative LOAEL for adult rats is considered to be equivocal evidence of adversity, thus the gap between adverse effects in rats and the dog NOAELs used for the POD may be even larger than 10x; (3) a 2-generation reproductive toxicity study in rats is not anticipated to report postnatal and reproductive-specific effects that could be attributed to a single dose exposure; and (3) given the differences in sensitivity between the dog and rat, the POD from the dog studies for all scenarios including inhalation is anticipated to be protective of the potential for increased postnatal sensitivity or reproductive toxicity in rats.

c. Chronic/Carcinogenicity Study

1. Background

Cancer risk was estimated for ethoxyquin in the 2004 Reregistration Eligibility Decision (RED) based on a theoretical upper bound Q_1^* (0.04 mg/kg/day^{-1}) derived from a Q_1^* predictor regression model of Q_1^* and MTD data for known carcinogens. The toxicologist used this approach because no guideline carcinogenicity studies were available, and this is a limited use chemical. The toxicologist also cited carcinogenicity evidence in a dermal study conducted with a chemical that was previously identified as a structural analog (discussed in Section III.c.4) and potential evidence of carcinogenicity in an ethoxyquin literature study (discussed in Sections III.c.8 and III.c.9) as factors in the decision to estimate a Q_1^*. This approach is quite conservative and assumes that ethoxyquin is a carcinogen. It was also stated in the RED that "[i]t must be strongly emphasized that we do not have any idea based on current data, whether ethoxyquin is a carcinogen or not, and if the determination of carcinogenicity is important to support a regulatory decision then the lack of cancer studies is a data gap. The approach used previously to estimate cancer risk in the absence of guideline carcinogenicity studies is not consistent with current practice, thus the requirement for the chronic/carcinogenicity toxicity study will be re-evaluated.

2. Physical Chemical Properties

TABLE 1. Physicochemical Properties		
Parameter	Value	Reference
Molecular Weight	217.34	
Melting point/range	Approximately 0° C	Sax and Lewis, 1987
pH	6.5	MRID 49636203
Density	1.03	MRID 49636203
Water solubility	170 ppm @ 25°C	MRID 43972301
Solvent solubility (temperature not specified)	Miscible with animal and vegetable fat and oils	Monsanto, 1959
Vapor pressure	2.60×10^{-4} mm Hg @ 25°C; 8.83×10^{-4} mm Hg @ 35°C; 2.49×10^{-3} mm Hg @ 45°C	MRID 43947401
Dissociation constant, pKa	No information found.	
Octanol/water partition coefficient, log P_{OW}	2.45 @ 25°C	MRID 43963201
UV/visible absorption spectrum	1.569-1.572 @ 25° C	Sax and Lewis, 1987

3. Mechanisms of Pesticide Activity

Ethoxyquin is an antioxidant. It does not target a specific pest species, rather its antioxidant properties deter the formation of scald on pear skin ("browning") and preserve animal feed and spices.

4. Read-across

In the cancer discussion for the Reregistration Eligibility Decision (RED), HED reported that ethoxyquin is structurally related to 1,2-dihydro-2,2,4-trimethylquinoline (Flectol H) – an antioxidant used in rubber manufacturing – and, to a lesser extent, quinoxaline-1,4-dioxide (quindoxin), a growth promoter for animal husbandry that is no longer on the market. After re-examining the structural relationship between these chemicals, it was determined that quindoxin is not a structural analog. Flectol H was more structurally similar to ethoxyquin than quindoxin and exhibited similar target tissues and toxicokinetic behavior; however, toxicity studies from the open literature on Flectol H demonstrate different toxicity behavior compared to ethoxyquin. Consequently, Flectol H is not considered a reliable structural analog for predicting ethoxyquin toxicity. The EPA CompTox Chemical Dashboard was used to identify structurally analogous chemicals and returned 28 chemicals that were $\geq$80% structurally similar to ethoxyquin. No mammalian toxicity data were available for these chemicals. Consequently, there are no relevant toxicity data from structural analogs to use in predicting the toxicity and/or carcinogenicity of ethoxyquin.

No relevant toxicity data were identified for structural analogs to use in predicting the toxicity and/or carcinogenicity of ethoxyquin.

5. Genetic Toxicity

Table 2. Summary of Mutagenicity and Genotoxicity Studies - Ethoxyquin

Guideline No./ Study Type/Animal Species and Strain	MRID No. or Study Authors (year)/ Classification /Doses	Results
870.5100 Bacterial reverse mutation *Salmonella typhimurium* (TA98, 100, 1535, 1537) *Escherichia coli* (WP2 *uvr*A)	46330701 (2004) **Acceptable/Guideline** 98.93% a.i. 10, 33, 100, 333, 1000, 2000, 3330, or 5000 ug/plate in DMSO w/ and w/o S9 fraction	**Negative** for mutagenicity in both presence and absence of metabolic activation
870.5300 *In vitro* mammalian cell gene mutation Mouse lymphoma assay	Study not submitted to EPA. Reported on the ECHA website[7] 5-25 µg/mL w/o S9 1.3-4.4 µg/mL w/ S9	**Positive** for clastogenicity with and without metabolic activation. No evidence of gene mutation.
870.5375 *In vitro* mammalian chromosomal aberration assay Chinese hamster ovary cells	46338901 (2004) **Acceptable/Guideline** 98.93% a.i. 9.69, 10, 13.8, 15, 19.8, 20, 25, and 28.2 µg/mL in DMSO w/ S9 fraction for 3 hours 28.2, 40.4, 57.6, and 82.4 µg/mL in DMSO (3-hour treatment) or 10, 15, 20, and 30 µg/mL in DMSO (20-hour treatment) w/o S9 fraction	**Positive** for structural chromosomal aberrations with and without metabolic activation.
870.5395 Mammalian erythrocyte micronucleus test Male Crl:CD-1(ICR)BR mice	46338501 (2004) **Acceptable/Guideline** 98.93% a.i. 24 hr prep: 0, 375, 750, or 1500 mg/kg via gavage (in corn oil) 48 hr prep: 0, 1500 mg/kg via gavage (in corn oil)	**Negative** for micronuclei induction in mice bone marrow cells up to 1500 mg/kg. *Clinical signs of toxicity were observed at dose ≥750 mg/kg including hypoactivity, squinted eyes, irregular respiration, ataxia, and/or a temporary trace. *Three mice in the 1500 mg/kg group died during the study

[7] https://echa.europa.eu/registration-dossier/-/registered-dossier/19351/7/7/1

Guideline No./ Study Type/Animal Species and Strain	MRID No. or Study Authors (year)/ Classification /Doses	Results
870.5550 *Ex vivo* unscheduled DNA synthesis test Rat hepatocytes collected from exposed animals	Study not submitted to EPA. Reported on the ECHA website. 0-750 mg/kg in two doses 14 hours apart	**Negative** for unscheduled DNA synthesis

Based on a weight of evidence of the available genotoxicity data, ethoxyquin is not of mutagenic concern. Although structural chromosome aberrations were induced in the *in vitro* mouse lymphoma and chinese hamster ovary cell cytogenetic assays, an analogous response was not demonstrated in *in vivo* bone marrow micronucleus assays in the mouse when tested up to 1500 mg/kg, a dose that induced overt toxicity.

6. ADME

A guideline metabolism and pharmacokinetics study was not available for ethoxyquin. The toxicokinetic behavior of ethoxyquin was, instead, evaluated based on information compiled from a number of published studies that covered the absorption, distribution, metabolism, and/or elimination of the compound in rodents.

Ethoxyquin is well absorbed across the rodent gastrointestinal tract, rapidly and extensively metabolized, and eliminated with varying efficiency depending on the dose level. A majority of the ingested ethoxyquin dose was absorbed in both rats and mice following a single dose exposure. At 24-hours post dose, absorption approached 61-69%, 50-57%, and 49-59% in rodents exposed to 2.5-25 mg/kg, 100 mg/kg, and 250 mg/kg, respectively, based on radioactivity in the urine only or urine and tissues combined (Sanders et al. 1996; Skaare & Solheim 1979). Absorption was higher than the urine data suggest, however, as biliary excretion was responsible for at least a portion of the radioactivity observed in feces (Skaare 1979; Sanders et al. 1996). For example, it accounted for approximately 36% of a 100 mg/kg oral dose (Skaare 1979) in rats indicating absorption was closer to 86-93% at that dose level. Absorption of ingested ethoxyquin was also rapid reaching peak blood concentration within an hour of exposure (Sanders et al. 1996). Peak concentration (Cmax), and area under the curve (AUC) were not reported in the literature.

Urine and biliary excretion were the primary routes of elimination regardless of dose level (Skaare & Solheim 1979; Sanders et al. 1996). Radioactivity in expired air was <1% of the administered dose (Skaare & Solheim 1979). Approximately 90% of the administered low oral dose (25 mg/kg) was accounted for in the feces and urine 24 hours post dose in both rats and mice. In contrast, only 60% of the administered high dose (250 mg/kg) was observed in excreta 24 hours after dosing. The differences in elimination behavior at the two dose levels suggest that toxicokinetics are non-linear at the high dose (250 mg/kg/day). By 48 hours, total elimination was comparable irrespective of dose (Sanders et al. 1996) and approximately 95% of the administered dose was accounted for in the excreta by 6 days post-exposure (Skaare & Solheim 1979). Elimination half-life from plasma was estimated to be 23 minutes (Sanders et al. 1996). Whole body elimination

half-life was not reported; however, the elimination data suggest the half-life is dose-dependent and longer at higher doses. Mice tended to eliminate ethoxyquin faster in feces; otherwise there were no differences in absorption and elimination between rodent species (Sanders et al. 1996).

Ethoxyquin-derived radioactivity distributed rapidly after absorption, primarily to tissues involved in elimination – liver and kidney – as well as adipose tissue (Sanders et al. 1996). It was also observed in the spleen, blood, and, to a lesser extent, heart, skeletal muscle, and brain. Ethoxyquin-derived radioactivity in liver, kidneys and adipose tissue accumulated with repeated exposure at both high (250 mg/kg) and low (25 mg/kg) dose levels; however, fold-increase (2-3X) in accumulation was generally higher in rodents fed the low dose (Sanders et al. 1996). Ethoxyquin-derived radioactivity were observed in the kidney, liver, lungs, and heart blood up to 6 days after exposure using whole-body radiography (Skaare & Nafstad 1979), but these persistent residues likely accounted for a small percentage of the administered dose given the near complete excretion observed at 6 days in a different study (Skaare & Solheim 1979). The authors suggested the persistence of residues in the body was likely due to storage and release of ethoxyquin-derived radioactivity from adipose tissue. Mice bioaccumulated less ethoxyquin-derived radioactivity in tissues compared to rats at comparable doses (Sanders et al. 1996).

Ethoxyquin is rapidly metabolized by rodents. Little to no parent compound was observed in feces and urine at 24 hours post exposure (Sanders et al. 1996). According to Burka et al. (1996), ethoxyquin undergoes oxidation and deethylation, and is then conjugated to endogenous compounds prior to excretion in the urine. Burka et al. (1996) identified two major ethoxyquin sulphate conjugated metabolites in rat urine and one major glucuronide metabolite in mouse urine. Rat biliary metabolites were primarily glutathione conjugates.

Ethoxyquin-associated radioactivity was observed in tissues up to 6 days after acute exposure, though it likely accounted for a small percentage of the administered dose as nearly 95% of the compound was eliminated in the excreta at that point. It is anticipated that ethoxyquin would persist in the body longer from repeat exposure based on the evidence of increased accumulation with multiple doses. Given this information, it is likely that toxicity in rats from longer term exposure would be greater than is predicted by the short-term studies. However, the ADME data also indicate that ethoxyquin toxicokinetics in rats are non-linear at doses $\geq$250 mg/kg/day and thus exposure at or above this dose level is not relevant for risk assessment. ADME information in the dog were not available to determine if ethoxyquin exhibited similar toxicokinetic behavior to rodents.

7. Acute Toxicity

Table 3. Acute Toxicity Profile - Ethoxyquin			
Guideline No.	**MRID (Year)/Classification**	**Results**	**Toxicity Category/Endpoints**
870.1100 Acute oral (rat)	43885901 (1995)	LD50 = 1726 mg/kg -Mortality observed at doses ≥1500 mg/kg, generally within 3 days of exposure -Mortality was preceded by clinical signs of toxicity	III
Non-guideline Acute oral (dog) Beagle dog	46336401 (2004) **Acceptable/Non-guideline** 98.93% a.i. 0, 50, 100, or 200 mg/kg via capsule in a single dose	-Dose dependent increase in bilirubin in urine, elevated ALT, and minimal to mild bile stasis observed at doses ≥50 mg/kg -Increase in bilirubin in blood above historical controls and elevated ALP at 200 mg/kg	NOAEL = 100 mg/kg/day LOAEL = 200 mg/kg/day based on increased bilirubin in blood and urine, elevated liver enzymes (ALT and ALP), glycogen depletion, and bile stasis.
870.1200 Acute dermal (rat)	43885902 (1995)	LD_{50} > 2000 mg/kg	III
870.1300 Acute inhalation (rat)	43894101 (1996)	LC_{50} > 1.97 mg/L	III
870.2400 Eye irritation (rabbit)	43885903 (1995)	Not an irritant	IV
870.2500 Dermal irritation (rabbit)	43885904 (1995)	Slight irritant	IV
870.2600 Skin sensitization	43885905 (1995)	Weak sensitizer	N/A

8. Sub-chronic Toxicity

Table 4. Subchronic Toxicity Profile - Ethoxyquin			
Guideline No.	**MRID (Year)/Classification**	**Results**	**NOAEL/LOAEL/Deficiencies**
870.3100 28-Day oral toxicity (rat) SD rats	44123801 (1996), 44222501 (1997) **Acceptable/Non-guideline** 98.2% a.i. 0, 50, 250, 500, or 1000 mg/kg/day via gavage (in corn oil) for 28 days	-At the 1000 mg/kg/day all animals died within 2-3 days preceded by agonal clinical signs of toxicity -Decreased RBC count, hemoglobin, and hematocrit at dose levels ≥250 mg/kg/day -Significant increase in serum calcium, cholesterol, total protein and globulin, and total bilirubin at doses ≥250 mg/kg/day -Significant increase in urea nitrogen, GGT, phosphorous, and potassium at 500 mg/kg/day -Significant increase in liver weight at doses ≥250 mg/kg/day -Dose dependent increase in incidence of kidney lesions (tubular dilation and tubular epithelium regeneration) in males at doses ≥250 mg/kg/day and in females at 500 mg/kg/day -Increase in incidence of hepatocellular swelling in females and lung hemorrhage in males and females at 500 mg/kg/day	NOAEL = 50 mg/kg/day LOAEL = 250 mg/kg/day, based on decreased hematology parameters (RBC count, hemoglobin, hematocrit), increased serum chemistry values (globulin, total protein, Ca, P, K, cholesterol), increased liver weights, and histopathological findings in the kidneys.
870.3100 90-Day oral toxicity (rat) SD rats	44123901 (1996) **Acceptable/Guideline** 98.2% a.i. 0, 20, 40, 200, or 400 mg/kg/day via gavage (in corn oil) for 90 days	-Decrease in body weight (10-14%) in males at doses ≥40 mg/kg/day that was not dose related -Decreased RBC, hematocrit and hemoglobin in both sexes at doses ≥200 mg/kg/day -Increased mean reticulocyte counts in females at ≥200 mg/kg/day and in males at 400 mg/kg/day -Decreased mean WBC counts at 400 mg/kg/day in both sexes -Increased serum albumin, globulin, and total protein in females at ≥200 mg/kg/day -Increase in total bilirubin, GGT, and cholesterol in both sexes at doses ≥200 mg/kg/day -Increased TSH at doses ≥200 mg/kg/day in males and 400 mg/kg/day in females, and decreased T4 in males at 400 mg/kg/day -Reddened and/or enlarged thyroid glands, increased liver and kidney weights at doses ≥200 mg/kg/day	NOAEL = 20 mg/kg/day LOAEL = 40 mg/kg/day based on decreased mean body weight gain in males.

Table 4. Subchronic Toxicity Profile - Ethoxyquin			
Guideline No.	**MRID (Year)/Classification**	**Results**	**NOAEL/LOAEL/Deficiencies**
		-Hyaline droplets in the cortical tubular epithelial cells and nephropathy in females at doses ≥200 mg/kg/day and renal papillary necrosis in both sexes at 400 mg/kg/day	
870.3150 28-Day oral toxicity (dog) Beagle	44149001 (1996) **Acceptable/Non-guideline** 98.2% a.i. 0, 25, 50, 100, or 200 mg/kg/day via capsule for 28 days	-All animals were sacrificed in extremis at 5-17 days at doses ≥100 mg/kg/day and one female mortality at 50 mg/kg/day -Sacrificed animals exhibited the following clinical signs: hypoactivity, ataxia, hypothermia, emaciation, pale gums, dermal atonia, green ocular discharge, decreased defecation, brown urine, severe body weight losses, and reduction in food consumption. -Reduced body weight in females at doses ≥25 mg/kg/day and in males at ≥50 mg/kg/day -Elevated ALP, ALT, AST, and GGT at doses ≥25 mg/kg/day -Dark livers, dilated vessel in heart, GI changes at doses ≥25 mg/kg/day -Moderate to severe endogenous pigment in liver at doses ≥25 mg/kg/day	NOAEL = not established LOAEL = 25 mg/kg/day based on decreased body weight gain in females, elevated ALP, ALT, AST and GGT enzyme levels and necropsy findings (dark liver, dilated vessel in the heart, GI changes, moderate to severe endogenous pigment on the liver).
870.3150 90-Day oral toxicity (dog) Beagle dog	44148901 (1996) **Acceptable/Guideline** 98.2% a.i. 0, 2, 4, 20, or 40 mg/kg/day via capsule for 90 days *Exposure in 40 mg/kg/day group ended at 49 days due to excessive systemic toxicity. The group remained on study for a six-week recovery and received empty gelatin capsules.	-Animals in 40 mg/kg/day group only exposed for 7 weeks then left on study to recover -Body weight loss at 40 mg/kg/day -Significantly increased total bilirubin, ALP, ALT, AST, and GGT at dose levels, and dark livers in nearly all animals at doses ≥20 mg/kg/day -Dose dependent increase in incidence of cytoplasmic vacuolation and minimal hepatocellular necrosis at 4 and 20 mg/kg/day -Endogenous pigmentation in liver observed at all groups with higher incidence at doses ≥20 mg/kg/day	NOAEL = 4 mg/kg/day LOAEL = 20 mg/kg based on elevated liver enzymes and total bilirubin, and macroscopic (dark livers) and microscopic findings in the liver (cytoplasmic vacuolation, minimal hepatocellular necrosis, bile duct hyperplasia).

Table 4. Subchronic Toxicity Profile - Ethoxyquin			
Guideline No.	**MRID (Year)/Classification**	**Results**	**NOAEL/LOAEL/Deficiencies**
870.3700a Prenatal developmental (rat) SD rats	44098901 (1996) **Acceptable/Guideline** 98.2% 0, 50, 150, or 350 mg/kg/day via gavage (in corn oil) across GD 6-19, inclusive	-Increased incidence of clinical signs of toxicity (wet yellow staining in the urogenital area, wet clear matting on the mouth, dried brown staining around the mouth) at 150 mg/kg/day	Maternal NOAEL = 50 mg/kg/day Maternal LOAEL = 150 mg/kg/day based on clinical signs of toxicity (wet yellow staining in the urogenital area, wet clear matting on the mouth, dried brown staining around the mouth) and reduced body weight gains and food consumption. Developmental NOAEL = 350 mg/kg/day Developmental LOAEL = not established.
Sub-chronic (diet) toxicity study Fisher 344 rats	Neal *et al*, 2003 Food Chem. Tox. **41**: 193-200 **Acceptable/Qualitative** 90% a.i. 0, 0.01, 0.05, 0.01, 0.25 or 0.5% (5, 25, 50, 125, or 250 mg/kg/day assuming 1 ppm is equivalent to 0.05 mg/kg/day in rats) for 3 or 6 months (5 males /group for 3 months feeding; 8/sex/group in the 6 month feeding except in the 0.05, 0.1, and 0.25% 5 females/group were used).	-At 5000 ppm (0.5% or 250 mg/kg/day) male rats exhibited either interstitial degeneration of the papilla or frank papillary necrosis after 3 and 6 months. Urothelial hyperplasia was also observed in males exhibited papillary necrosis at 6 months. -Similar findings not reported at 2500 ppm (0.25% or 125 mg/kg/day) or lower dose. In the female rats, 6 months of feeding produced early minimal interstitial degeneration in one individual only at the 0.5% exposure level. -When C-14 ethoxyquin was administered ip or orally by gavage (10 mg/kg), the radiolabel was associated with urinary albumin. The ratio of the excreted radioactivity in the urine to feces was 7.3-8.2. Autoradiographic sections of the kidneys did not show differences among the sexes in the distribution of the radioactivity or retention of ethoxyquin. Fecal and urinary metabolites' profiles were similar in the two sexes. No un-metabolized ethoxyquin was detected in any sample. Treatment of the urine and fecal extracts with β-glucuronidase failed to produce any detectable level of non-polar labeled compounds.	NOAEL = 0.25% (125 mg/kg/day) LOAEL = 0.5% (250 mg/kg/day) based on interstitial degeneration of papilla, papillary necrosis, and urothelial hyperplasia

Table 4. Subchronic Toxicity Profile - Ethoxyquin			
Guideline No.	**MRID (Year)/Classification**	**Results**	**NOAEL/LOAEL/Deficiencies**
Subchronic (dietary) toxicity study 3 and 8-week old F344 rats	Manson *et al*, 1992. Arch Toxicol 66(1):51-56 **Acceptable/Qualitative** 90% a.i. 0 or 0.5% (estimated at 0 or 250 mg/kg/day assuming 1 ppm is equivalent to 0.05 mg/kg/day in rats) in arachis oil in diet for 20-26 weeks	-Female rats were much less susceptible to the toxic effects of ethoxyquin than males of the same age. -Males exhibited an increase in absolute kidney weight and both sexes exhibited a significant increase in relative kidney weight, with a greater increase observed in males. -In males damage to the cortex (eosinophilic cytoplasmic inclusions in tubular epithelial cells, protein accumulation in lumina of tubules, thickening of basement membranes around tubules and Bowman's capsules and hyperplasia of pelvic transitional epithelium) was similar in both age groups. -Treated males exhibited an increase in BrdU labelling in epithelial tubule cells both in regenerating basophilic tubules typical of aging lesions and in mildly hyperplastic tubules. -In addition, rats exposed to ethoxyquin as weanlings suffered from extensive papillary necrosis and one animal exhibited severe calcification in the papilla. Pyelonephritis was also observed in two males from the weanling treatment groups but was considered incidental by the study authors and attributed to bacterial infection. Older males (8-weeks of age at the start of exposure) exhibited a reduction or complete loss of GGT enzyme activity in a number of tubules after 20 weeks of exposure. One older male also exhibited papillary necrosis and another loss of interstitial cells at papillary tip after 30 weeks of exposure. -Male rats were more prone than females to proteinuria, which was greatly exacerbated by ethoxyquin in both age groups. -There is very little evidence of nephrotoxicity in adult female rats on exposure to ethoxyquin at 0.5% in the diet for 26 weeks. In males, the initial age of the animal, as well as the length of treatment, influences the extent of damage	NOAEL = not established LOAEL = 0.5% (250 mg/kg/day) based on increased kidney weight, damage to renal cortex (including transitional epithelium hyperplasia), papillary necrosis, and proteinuria Deficiencies: Single dose tested
Subchronic (dietary) toxicity study	Manson *et al*, 1987; Carcinogenesis; 8:723-728 **Acceptable/Qualitative**	-Liver weight was significantly elevated in both ethoxyquin treatment groups at the end of the 23-week period. -Ethoxyquin in the diet completely prevented the formation of AFB1-induced preneoplastic liver lesions as judged by morphological alteration,	NOAEL = not established LOAEL = 0.5% (250 mg/kg/day) based on increased liver weight, hyperplastic and putative preneoplastic renal tubules

Table 4. Subchronic Toxicity Profile - Ethoxyquin			
Guideline No.	**MRID (Year)/Classification**	**Results**	**NOAEL/LOAEL/Deficiencies**
F344 rats	95% a.i. 0 or 0.5% ethoxyquin (estimated at 0 or 250 mg/kg/day assuming 1 ppm is equivalent to 0.05 mg/kg/day in rats) in diet for 23 weeks with or without aflatoxin.	or by markers such as gamma glutamyl transpeptidase, glutathione S-transferase P or J1, an unknown membrane-bound antigen. -No preneoplastic liver lesions were observed in the animals on the ethoxyquin only diet. -Kidney weight was not significantly different from controls, but ethoxyquin treated animals did exhibit characteristics of chronic glomerulonephritis, that are normally observed in older animals. -In addition, hyperplastic and putative preneoplastic tubules were visible with many containing brown pigment (staining suggested it was lipofuscin) and mitotic figures. -Pigment-bearing hyperplastic tubules exhibited GB-ase activity and a reduction or complete loss of GGT activity. GST-P, usually localized to specific areas of cortex, was extend to the whole cortex in ethoxyquin treated animals and exhibited variable activity in basophilic tubules and tubules with flattened epithelia.	Deficiencies: Single dose tested, low animal numbers, all kidney findings were presented qualitatively without details on the incidence or severity, and numerical values were not presented for the enzyme activity assessments in the kidneys.

There is clear progression of toxicity from single dose (Section 8) to repeat dose exposure in both rat and dogs. Based on the guideline studies and chronic dog information in an EFSA report, there does not, however, appear to be a progression of toxicity in the dog with increasing exposure duration in repeat dose studies. Therefore, the liver and body weight toxicity described in the subchronic dog studies are also anticipated to occur at similar dose levels following chronic exposure. In rats, the guideline and literature studies provided information on subchronic toxicity for up to 26 weeks of exposure. There was no evidence of progression between 4 and 13 weeks of exposure in rats; however, it is difficult to determine if there is progression of toxicity beyond 13 weeks of exposure given that most of the longer duration studies only examined a single dose level. Given this uncertainty, it is unclear how useful the rat guideline subchronic studies are for predicting chronic toxicity. The literature studies, on the other hand, do provide some information on longer-term exposure at high doses which is useful for evaluating chronic exposure and carcinogenic potential. There was evidence of renal (urothelial/transitional epithelium) hyperplasia in rats across the literature studies at dietary doses up to 250 mg/kg/day and exposure duration from 23 to 26 weeks (Manson et al. 1987; Manson et al. 1992; Neal et al. 2003). No renal tumors were observed in these studies. Although this information is useful, there are some issues with using the literature studies to predict chronic toxicity. First, these literature studies were focused primarily on kidney toxicity, and did not explore the impact of ethoxyquin exposure on other tissues with one exception (Manson et al. 1987). Second, most studies were conducted at a single dose, thus the dose-response relationship of the observed effects could not be evaluated. Finally, all of these studies used fewer than the recommended number of animals for evaluating chronic toxicity and carcinogenicity.

The subchronic studies present information that is useful for predicting chronic toxicity and carcinogenicity. The guideline subchronic dog studies, in particular, were considered relevant for assessing chronic exposure based on evidence that suggests a lack of progression with exposure duration in repeat dose studies. In contrast, there is uncertainty as to whether progression occurs in the rat. There was no evidence of progression between the 4 and 13-week exposures in rats; however, the ADME suggests that there is the potential for greater toxicity from longer duration repeat dose exposures due to increased accumulation of ethoxyquin-derived radioactivity. Thus, the shorter term rat subchronic studies (i.e. 4 and 13-week guideline studies) are considered less reliable for predicting chronic toxicity. The literature subchronic rat studies, on the other hand, report toxicity information for gavage and dietary doses up to 250 mg/kg/day for 26 weeks. Although the literature studies have some deficiencies, these studies consistently reported kidney effects including urothelial hyperplasia and papillary necrosis after dietary exposure to 250 mg/kg/day for 20-26 weeks. These potential preneoplastic findings suggest potential for carcinogenicity at this dietary dose level; however, there was no evidence of tumors from dietary exposure up to 26 weeks. It should also be noted that the ADME suggest the toxicokinetics for ethoxyquin are non-linear at 250 mg/kg/day indicating that the effects observed at or above this dose level are not relevant for risk assessment.

Based on the data from the guideline and literature studies, dogs are more sensitive to ethoxyquin exposure compared to rats. The points of departure (PODs) selected for risk

assessment were thus based on the subchronic dog study. Given the lack of progression in the dog, the subchronic study was considered appropriate for use as the chronic dietary POD. Although there is some uncertainty as to whether toxicity in rats progresses with duration, rats would have to be at least 10x more sensitive to chronic exposure for the current chronic POD to no longer be protective.

9. Literature Chronic Toxicity and Carcinogenicity

Table 5. Chronic Toxicity Profile - Ethoxyquin			
Guideline No.	**MRID (Year)/Classification**	**Results**	**NOAEL/LOAEL/Deficiencies**
Chronic (dietary) toxicity study Albino rats	MRID 05000474 Wilson and DeEds 1959; Monsanto, 1985 **Unacceptable** Did not report % a.i. **Trial I**. 10 rats/sex/group at 0, 0.2%, 0.4%, ETX (0, 100 or 200 mg/kg/day) for 200 days. **Trial II.** 10 males/group at 0, 0.0062%, 0.0125%, 0.05%, 0.1%, 0.2% (3, 6, 25, 50, or 100 mg/kg/day) and 10 females/group at 0, 0.05%, 0.1%, 0.2% ETX for 225 days. **Trial III.** 10 rats/sex/group at 0, 0.0062%, 0.0125%, 0.05%, 0.1%, 0.2% (3, 6, 25, 50, or 100 mg/kg/day) for 200, 400, 600, or 715 days.	-Males and females from 0.2% and 0.4 % ETX groups weighed significantly less ($p<0.05$-0.01) than controls. -Liver weights among females in the 0.2% ETX group and males in the 0.1% group as well as liver weights in all higher dose groups were significantly greater ($p<0.01$) than controls. -Kidneys weights were significantly greater ($p<0.01$) in the 0.2% and 0.4% dose groups versus controls. -Kidneys of 2 male rats in the 0.4% ETX group, had stones in the renal pelvis. Microscopic examination revealed well-developed chronic pyelonephritis among males at $\geq$0.2% ETX. Two kidneys had areas of calcification. -The thyroid glands of male rats exposed to 0.4% ETX had evidence of hyperplasia. -All male rats in the 0.2% ETX group, 3/4 in the 0.1% group, and 2/5 in the 0.05% group had small kidney scars. -Occasional tumors that were unrelated to dose level and similar to concurrent controls	Classified unacceptable due to inadequate characterization of the test material and number of animals tested.

Table 5. Chronic Toxicity Profile - Ethoxyquin			
Guideline No.	**MRID (Year)/Classification**	**Results**	**NOAEL/LOAEL/Deficiencies**
Chronic (dietary) toxicity study Fisher 344 rats	Hard & Neal, 1992 Fund. Appl. Tox. **18**: 185-189 **Acceptable/Qualitative** 90% a.i. 0 or 0.5% ethoxyquin (65.5/70.6 mg/kg/day for males/females based on body weight and diet consumption rate provided by authors) in arachis oil in diet for 4, 12-14, 24, 58 weeks or 18 months.	-Body weight gain in treated rat was 80%/ 90% of controls for males/females, feed consumption not affected. -Interstitial degeneration of the extremity of the renal papilla was seen in male rats after 4 weeks which progressed to necrosis and pyelonephritis with loss of part of the papilla and foci of mineralization in the abscission layer by week 24. -All treated male rats at 58 weeks had papillary necrosis, pyelonephritis, urothelial hyperplasia, and moderately severe chronic progressive nephropathy. -At 18 months, all treated males had complete papillary necrosis with tissue loss and severe end stage chronic progressive nephropathy. Although the incidence was greater at this time point, the authors indicate there was evidence of healing in the truncated papillae, there were fewer foci of active inflammation, fewer basophilic hyperplastic tubules associated with pyelonephritis, and less marked hyperplasia with papillary necrosis compared to previous sampling times -Papillary degeneration in female rats was not observed until 12 to 14 weeks of exposure and the incidence increased with exposure duration. -At 58 weeks, eight of nine females had varying degrees of papillary tip interstitial degeneration, five exhibited mild pyelonephritis, and one exhibited low-grade urothelial hyperplasia. -By 18 months, all treated females had interstitial degeneration of the papillary tip, but the lesion had not progressed beyond the earlier stage. Unlike males, none of the treated females exhibited papillary necrosis throughout the exposure period. Mild urothelial hyperplasia was also observed in two of 13 females at 18 months, but there were no signs of pyelonephritis in females at this point. -The authors considered the pyelonephritis and urothelial hyperplasia to be secondary response related to the papillary necrosis and not a direct reaction to ethoxyquin.	NOAEL = not established LOAEL = 0.5% (65.5/70.6 mg/kg/day in males/females) based on kidney lesions including papillary necrosis, pyelonephritis, urothelial hyperplasia, and accelerated chronic progressive nephropathy Deficiencies: Single dose tested, inadequate number of animals for chronic/carcinogenicity testing

Table 5. Chronic Toxicity Profile - Ethoxyquin			
Guideline No.	**MRID (Year)/Classification**	**Results**	**NOAEL/LOAEL/Deficiencies**
Initiation/ Promotion study Female SD rats (mammary and ear duct tumors) F344 rats (liver and kidney tumors)	Ito et al. 1986 **Acceptable/Qualitative** % ai not reported (described as food additive grade and assumed to be >90% based on source) 0 or 0.8% (estimated at 0 or 400 mg/kg/day assuming 1 ppm is equivalent to 0.05 mg/kg/day in rats) for 29-33 weeks *Mammary and ear duct tumor study: Subset of animals exposed to single 25 mg/kg gave dose of 7,12-dimethylbenz[*a*]anthracene (DMBA) prior to ethoxyquin exposure **Kidney and liver tumor study: Subset of animals exposed to 0.1% N-ethyl-N-hydroxyethylnitrosamine (EHEN) for 2 weeks in	-No evidence of an increase in mammary or ear-duct tumors from exposure to 0.8% ethoxyquin in the diet 33 weeks. -Dietary ethoxyquin exposure after 2-week exposure to DMBA resulted in a significant decrease in incidence of mammary carcinomas and fibroadenomas and a non-significant decrease in ear duct carcinomas and adenomas compared to DMBA exposure followed by basal diet. -No evidence of increase in liver hyperplasic nodules or hepatocellular carcinomas nor kidney adenoma or adeno-carcinomas from exposure to 0.8% ethoxyquin alone in the diet 29 weeks. -Dietary ethoxyquin exposure after 2-week exposure to 0.1% EHEN resulted in an increase in incidence of kidney adenomas and decrease in incidence of hepatocellular carcinomas compared to EHEN exposure followed by basal diet.	NOAEL = 0.8% LOAEL = not established Deficiencies: Single dose tested, inadequate number of animals for chronic/carcinogenicity testing (25 animals/experiment)

Table 5. Chronic Toxicity Profile - Ethoxyquin			
Guideline No.	**MRID (Year)/Classification**	**Results**	**NOAEL/LOAEL/Deficiencies**
	drinking water prior to ethoxyquin exposure		
Chronic (subcutaneous injection) toxicity study Swiss albino mice	Epstein et al. 1970 **Unacceptable** Did not report % a.i. 0, 6*, or 30** mg ethoxyquin administered in weekly subcutaneous doses on PND1, 7, 14, and 21 *1 mg administered on PND1 and 7 and 2 mg administered on PND14 and 21 for total of 6 mg **5 mg administered on PND1 and 7 and 10 mg administered on PND14 and 21 for total of 30 mg	-74% mortality in the 30 mg treatment group prior to weaning. An additional 4 males and 2 females from this treatment group died after weaning. -Pulmonary adenomas (M:4/9 and F:1/5) and lymphomas (M:2/5 and F:2/9) above concurrent controls were observed in females and males from the 30 mg treatment group. -One instance of multiple pulmonary adenomas was observed in males from the 30 mg treatment group.	Classified unacceptable due to inadequate characterization of the test material, route of administration, and number of animals tested.

No guideline chronic/carcinogenicity studies are available to assess the carcinogenic potential of ethoxyquin in laboratory models; however, there are a number of studies in the open literature that investigated toxicity from chronic exposure or reported on the carcinogenic potential of ethoxyquin. It is important to note that most of the open literature studies evaluated the tumor promoting potential of ethoxyquin and as a result, investigated only a single dose level of ethoxyquin and the one or two tissues that were relevant to the known carcinogen (tumor initiator). The duration of exposure also varied from study to study. These studies did indicate that ethoxyquin may potentiate or inhibit the activity of some carcinogens but lacked robust carcinogenicity data for ethoxyquin only exposures. Also, with two exceptions, these studies either were not accessible or were classified unacceptable for use in risk assessment primarily due to inadequate characterization of the test material. The first exception, Manson et al (1987), is discussed in more detail in the subchronic section above. The other exception is a study by Ito et al. (1986). The authors investigated the potential tumor promotion activity of ethoxyquin for several known carcinogens and in variety of tissues. However, toxicity/carcinogenicity data for ethoxyquin only exposure were limited to investigations in the liver, kidney, ear duct, and mammary tissues. The authors did not report any tumors (adenomas or carcinomas) in these tissues following dietary exposure to ~400 mg/kg/day for 29-33 weeks. Confidence in the study results is diminished by the use of a single dose level and using fewer than the recommended number of animals (25 animals/experiment) for carcinogenicity testing. Few literature studies were designed to specifically examine the chronic toxicity/carcinogenicity of ethoxyquin and those that were available for review contained deficiencies (some critical) that limited their utility for risk assessment. Hard and Neal (1992) reported papillary necrosis, pyelonephritis, urothelial hyperplasia and chronic progressive nephropathy after 18 months of exposure to 250 mg/kg/day in the diet. No renal tumors were reported. The authors concluded that the hyperplasia was likely secondary to papillary necrosis given the concordance of the two lesions and the parallel observation of a reduction in severity of the hyperplasia and healing of papillary stump in rats exposed for 18 months. The results of this study align with the subchronic literature information discussed above; however, it is hindered by some of the same deficiencies that limited the utility of those data including using fewer than the recommended number of animals (6-20/sex) for chronic/carcinogenicity testing, reporting toxicity in the kidneys only, and testing a single dose level. The results of this study nevertheless suggest that exposure for up to 250 mg/kg/day for 18 months does not elicit renal carcinogenicity. Another chronic ethoxyquin study from the literature (Wilson and DeEds 1959) was added to the ethoxyquin database to support the Reregistration Eligibility Decision. The study investigated dietary exposure in rats across multiple dose levels (3-200 mg/kg/day) for up to 2 years. All effects reported in the study occurred at doses $\geq$25 mg/kg/day. The authors reported occasional tumors in all groups that were unrelated to exposure; however, the study used only 10 rats/sex/dose which is unacceptable for a cancer assay. Furthermore, the publication did not adequately characterize the test material rendering the data of limited use to evaluating chronic toxicity and carcinogenicity for risk assessment. A final study (Epstein et al. 1970) identified in the open literature exposed rat neonates to ethoxyquin (6 or 30 mg total) via four weekly subcutaneous injection during weaning. This study reported high mortality in the 30 mg treatment group. Pulmonary adenomas and lymphomas above concurrent controls were observed in females and males from the 30 mg treatment group. One instance of multiple pulmonary adenomas was observed in males from the 30 mg treatment group. This study also used few than recommended number of animals, did not

report purity, and explored a route of administration that is not relevant to risk assessment. This information is also of limited use to risk assessment.

The literature chronic studies that explored carcinogenicity of ethoxyquin generally focused on one or a few tissues, used a single dose, and used fewer than the recommended number of animals for a carcinogenicity assessment. Kidney toxicity including papillary necrosis and urothelial hyperplasia was observed in one study after dietary exposure to ~65 mg/kg/day for 58 – 72 weeks that was consistent with the findings in the subchronic studies; however, there were no renal tumors observed up to 72 weeks. Similarly, there was no evidence of adenomas or carcinomas in the kidney, liver, ear duct, or mammary tissue from dietary exposure to ~400 mg/kg/day for 29-33 weeks. These findings suggest that although there is evidence of preneoplastic lesions, it does not progress to tumors from longer exposure at least at the dose levels tested and within the dose range that the ADME suggests follows linear toxicokinetics. The remaining literature studies (including those that investigated the inhibition/potentiation of other carcinogens) were either not available or were unacceptable for use in risk assessment, usually due to inadequate characterization of the test material.

10. Evidence of Hormone Perturbation

None of the studies in the ethoxyquin toxicity database nor the acceptable studies identified in the open literature were designed with a specific focus on hormone perturbation. Nevertheless, none of these studies reported general evidence of estrogenic effects following ethoxyquin exposure. There was evidence of chemical-induced thyroid hormone fluctuations and increased thyroid weight in the guideline rat subchronic study; however, the effects were observed at a dose level that was 50X above the current chronic POD.

There is limited information available to evaluate the potential for ethoxyquin to perturb the estrogen or thyroid hormone systems. Based on the available data, there is no evidence to suggest that ethoxyquin will elicit carcinogenicity from hormone perturbation at the regulatory dose levels. Guideline studies and acceptable open literature studies did not report estrogenic effects from ethoxyquin exposure and the current chronic POD is protective of the thyroid hormone perturbations observed in rats following oral exposure.

11. Evidence of Immune Suppression

A guideline immunotoxicity study was not conducted for ethoxyquin because the HASPOC recommended the requirement be waived at a previous meeting (TXR 0053945, J. Leshin, 08/21/2014). None of the studies in the ethoxyquin toxicity database nor the acceptable studies identified in the open literature were designed to investigate immunotoxicity. Some of these studies did, however examine parameters that could indicate a chemical induced change in immune system function. Changes in leukocyte levels were observed in dogs following oral ethoxyquin exposure for 90 days; however, there was no evidence of organ weight changes or abnormal histological findings in tissues associated with the immune system. These changes were also within the historical control levels. There were no findings in the rat guideline studies indicating toxicity in the immune system. Only one immunotoxicity focused study was identified

in the open literature and it was determined to be unacceptable for risk assessment. The acceptable open literature studies did not focus on toxicity in the immune system but did report an increased incidence of kidney infection (pyelonephritis) in rats exposed to dietary concentrations of ethoxyquin of 65-250 mg/kg/day for 20-72 weeks. The authors attributed the increase in this finding in ethoxyquin exposed rats to the increase in papillary necrosis observed at the same dose level rather than a suppression of the immune system. There were no other indications of immune system toxicity in the open literature studies.

Although an immunotoxicity guideline study was not available, there was no evidence in the guideline studies or open literature to suggest ethoxyquin suppresses the immune system.

12. Proposed Points of Departure, and Prospective Risk Assessments

Chronic dietary exposure is anticipated from food sources only. Adequate label restrictions regarding wash-water recycling practices are anticipated to prevent ethoxyquin from reaching drinking water sources. Occupational exposure is anticipated to be intermittent based on the use pattern and long-term/chronic occupational exposures are not anticipated; however, the anticipated exposure scenarios do align with the exposure assumptions used for the occupational cancer assessment (i.e. either 10 or 30 days/year for 35 of 70 years).

The nature of the residue in pear reflecting post-harvest use of ethoxyquin is adequately understood. The residue of concern in/on pear for enforcement is parent only (Metabolism Committee 12/20/94). The ethoxyquin risk assessment team has determined that the residues of concern in/on pear for risk assessment are parent and its C-N and N-N dimers. Data, though limited, suggest that the dimers are not more toxic than the parent. The current tolerance level for pears is 3 ppm and monitoring data for ethoxyquin (USDA PDP) found detectable residues in 27.4% of fresh pears taken close to the time and point of consumption (i.e., distribution centers rather than at the processing plant) and which have been rinsed; residues of ethoxyquin ranged from 0.01 – 2.3 ppm. In addition, tolerances are established by FDA for several spices, as well as, meat, milk, poultry, and egg due to tolerances they established in livestock/fish feed. Based on limited available livestock data, parent is the major residue in livestock. Based on published data, parent and its C-N dimer are the major residues in fish. Based on published data, an estimate for residues of concern in fish was included in the dietary analyses. Pear is the major contributor to the dietary cup. Using the NOAEL from the guideline subchronic dog study as the POD, unrefined chronic dietary risk from all sources of ethoxyquin is 21% of the chronic PAD.

13. Recommendation

Given the available information and the known differences in species sensitivity, it is not anticipated that a rat chronic study would provide a lower POD than the current chronic dietary POD based on the subchronic dog study. With respect to carcinogenicity acceptable literature studies suggest that oral ethoxyquin exposure up to 250 mg/kg/day in the diet for 26 weeks, 400 mg/kg/day for 29 weeks, and 65 mg/kg/day for 72 weeks do not elicit renal tumors, despite the kidney being a target organ with evidence of necrosis and urothelial hyperplasia. There was also no evidence of liver tumors (another target organ in rats) from dietary exposure to 400

mg/kg/day for 29 weeks, nor ear duct or mammary tumors from dietary exposure to 400 mg/kg/day for 33 weeks. There is some uncertainty in these findings as they are based on results from a single dose level, the studies used fewer than the recommended number of animals for carcinogenicity testing, and they were not designed to be as comprehensive as a guideline carcinogenicity study. Nevertheless, these findings indicate a low concern for carcinogenicity at the doses tested as well as within the dose range relevant for risk assessment based on the toxicokinetics (i.e. ADME suggest non-linear kinetics at dose levels $\geq$250 mg/kg/day). There is also no concern for mutagenicity *in vivo* based on data from guideline mutagenicity studies. In terms of sensitivity, liver toxicity in the dog occurred at doses at least 3X lower than the dietary dose eliciting the chronic renal effects in rats. Furthermore, the current POD based on the liver toxicity in the dog is 16X lower than the lowest dose eliciting renal effects in rats indicating it is protective of the preneoplastic lesions.

Based on a WOE approach, considering all the available ethoxyquin hazard and exposure data, the HASPOC recommends that a chronic/carcinogenicity study be waived at this time. This approach included the following considerations: (1) no concern for mutagenicity *in vivo*; (2) while there was evidence of preneoplastic lesions, there was no evidence of tumorgenicity at ethoxyquin dietary doses that fall within or above the dose range that the ADME suggests follow linear toxicokinetics; (3) there is no evidence of immune suppression in the toxicity database or open literature; (4) the dog is more sensitive to ethoxyquin exposure than rats which are traditionally used in the chronic toxicity/carcinogenicity guideline study; (5) rats would have to be at least 10x more sensitive to chronic exposure to exhibit effects at a dose similar to or lower than the current chronic POD; (6) using the chronic POD from the dog studies for all scenarios including inhalation is anticipated to be protective of chronic effects in the rat including the preneoplastic renal effects reported in the literature and the thyroid effects reported in the subchronic guideline study; (7) dietary exposure to ethoxyquin is primarily from pears with a minor contribution from food preservative uses registered by FDA; and (8) based on the limited use pattern (post-harvest pears) long-term/chronic occupational exposures are not anticipated.

IV. HASPOC CONCLUSIONS

Based on a WOE approach, considering all the available hazard and exposure data for ethoxyquin, the HASPOC recommends that the non-rodent developmental, 2-generation reproduction, and chronic/carcinogenicity studies for ethoxyquin be waived at this time.

V. APPENDIX A

A.1 Ethoxyquin Endpoint Table

Table A.1.1. Summary of Toxicological Doses and Endpoints for Ethoxyquin for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	POD	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations, including Infants and Children)	NOAEL = 100 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Acute RfD = 1 mg/kg/day aPAD = 1 mg/kg/day	Non-guideline acute oral – dog MRID 46336401 LOAEL = 200 mg/kg/day based on elevated liver enzyme levels, bile stasis accompanied by increased bilirubin in blood and urine, increased leukocytes and depleted liver glycogen
Chronic Dietary (All Populations)	NOAEL = 4 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Chronic RfD = 0.04 mg/kg/day cPAD = 0.04 mg/kg/day	Subchronic oral study – dog MRID 44148901 LOAEL = 20 mg/kg/day based on elevated liver enzymes and total bilirubin, dark appearance of the liver, and microscopic findings in the liver (bile duct hyperplasia, cytoplasmic vacuolation and hepatocellular necrosis).
Cancer (oral, dermal, inhalation)	Ethoxyquin is classified as "Inadequate Information to Assess Carcinogenic Potential". A non-linear approach (i.e., RfD) would adequately account for all the chronic toxicity, including the preneoplastic lesions, that could result from exposure to ethoxyquin.			

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table A.1.2. Summary of Toxicological Doses and Endpoints for Ethoxyquin for Use in Occupational Human Health Risk Assessments.				
Exposure/ Scenario	**POD**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- and Intermediate-Term (1 day - 6 months)	NOAEL = 4 mg/kg/day DAF= 8%	UF_A = 10X UF_H = 10X	Occupational LOC for MOE = 100	Subchronic oral study – dog MRID 44148901 LOAEL = 20 mg/kg/day based on elevated liver enzymes and total bilirubin, dark appearance of the liver, and microscopic findings in the liver (bile duct hyperplasia, cytoplasmic vacuolation and hepatocellular necrosis).
Inhalation Short- and Intermediate-Term (1 day - 6 months)	NOAEL = 4 mg/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE = 100	Subchronic oral study – dog MRID 44148901 LOAEL = 20 mg/kg/day based on elevated liver enzymes and total bilirubin, dark appearance of the liver, and microscopic findings in the liver (bile duct hyperplasia, cytoplasmic vacuolation and hepatocellular necrosis).
Cancer (oral, dermal, inhalation)	Ethoxyquin is classified as "Inadequate Information to Assess Carcinogenic Potential". A non-linear approach (i.e., RfD) would adequately account for all the chronic toxicity, including the preneoplastic lesions, that could result from exposure to ethoxyquin.			

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

A.2 Dietary Risk Estimate Table

Table A.2.1. Summary of Preliminary Estimates for Dietary (Food Only) Exposure and Risk for Ethoxyquin.						
Population Subgroup	**Acute Dietary (95th Percentile)**		**Chronic Dietary**		**Cancer**	
	Dietary Exposure (mg/kg/day)	**% aPAD***	**Dietary Exposure (mg/kg/day)**	**% cPAD***	**Dietary Exposure (mg/kg/day)**	**Risk**
General U.S. Population	0.009986	1.0	0.003502	8.8	Not Analyzed	
All Infants (<1 year old)	**0.028123**	**2.8**	0.004814	12		
Children 1-2 years old	0.024718	2.5	**0.008428**	**21**		
Children 3-5 years old	0.020291	2.0	0.007629	19		
Children 6-12 years old	0.013853	1.4	0.005131	13		
Youth 13-19 years old	0.008808	<1	0.003189	8.0		
Adults 20-49 years old	0.008060	<1	0.003032	7.6		
Adults 50-99 years old	0.007126	<1	0.002668	6.7		
Females 13-49 years old	0.007261	<1	0.002576	6.4		

A.3 Occupational Risk Estimate Tables

Thermal Fogging Applications:

Table A.3.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Ethoxyquin.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai)[1]	Level of PPE or Engineering control	Inhalation Unit Exposure (µg/lb ai)[1]	Level of PPE or Engineering control	Maximum Application Rate[2]	App Rate Unit	Area Treated or Amount Handled Daily[3]	Area Treated/Amount Handled Unit	Dermal		Inhalation		Total
										Dose (mg/kg/day)[4]	MOE[5]	Dose (mg/kg/day)[6]	MOE[7]	MOE[8]
Mixer/Loader														
Liquid, Stationary/Automatic Fogger/Mister (with re-entry restriction), Broadcast	Treatment Facility (Post-Harvest Pears)	37.6	SL/G	0.219	No-R	0.0000107	lb ai/lb fruit	144000	lbs fruit	0.0000579	69000	0.00000421	950000	64000

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of mitigation: Label-Required PPE: SL/G.
2 Based on registered label (Reg. No. 64684-60).
3 Exposure Science Advisory Council Policy #9.1.
4 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/lb fruit) × Area Treated or Amount Handled Daily (lbs fruit/day) × DAF (8%) ÷ BW (80kg).
5 Dermal MOE = Dermal NOAEL (4 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (80 kg).
7 Inhalation MOE = Inhalation NOAEL (4 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
8 Total MOE = NOAEL (4 mg/kg/day) ÷ Dermal Dose + Inhalation Dose **OR** Total MOE = 1 ÷ (1/Dermal MOE + 1/Inhalation MOE).

Post-Harvest Drench or Spray Treatment Applications:

Table A.3.2. Occupational Handler Short- and Intermediate-Term Exposure and Risk Estimates for Post-Harvest Uses of Ethoxyquin.

Exposure Scenario	Application Rate (lb ai/gal soln)[1]	Amount ai Handled (gal solution)[2]	Dermal Unit Exposure		Inhalation Unit Exposure (No-R)[3]	Dermal Dose (mg/kg/day)[4]	Inhalation Dose (mg/kg/day)[5]	Dermal MOE[6] (LOC=100)	Inhalation MOE (LOC =100)[7]	Total MOE[8]
			µg/lb ai[3]	Level of Protection						
Mixing/Loading Liquids for Post-Harvest Treatment in an Automated System	0.022	25,000	37.6	SL/G	0.219	0.021	0.00151	190	2700	180
			29.1	DL/G	0.219	0.016	0.00151	250	2700	230
Mixing/Loading/Applying Liquids for Post-Harvest Treatment via Mechanically Pressurized Handgun Equipment (In Line Spray)	0.022	1,000	2,050	SL/G	8.68	0.045	0.00239	**89**	1700	**85**
			1,360	DL/G	8.68	0.03	0.00239	130	1700	120

1 Maximum application rate based on representative label (Reg. No. 64864-58) 3.91 lb ai /gallon product, dilution for 2700ppm = 1:175 concentrate to water.
2 Based on ExpoSAC Policy/Guidance "Assessment of Occupational Exposure for Post-Harvest Commodity Pesticide Treatments" (M. Crowley, FEB-2018); Level of mitigation: SL/G = label required PPE for sorter/packers.
3 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of mitigation: Label-Required PPE: SL/G.
4 Dermal Dose (mg) = [UE (mg/lb ai) * AaiH (lb ai) * AF(8%)] ÷ BW (80 kg); and Dermal Dose = [UE (mg/lb ai) * AR (lb ai/gallon) * AVH (gallons) * AF(8%)] ÷ BW (80 kg).
5 Dermal MOE = Dermal NOAEL (4 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose (mg) = [UE (mg/lb ai) * AaiH (lb ai) * AF] ÷ BW (80 kg); and Inhalation Dose = [UE (mg/lb ai) * AR (lb ai/gallon) * AVH (gallons) * AF] ÷ BW (80 kg).
7 Inhalation MOE = Inhalation NOAEL (4 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
8 Total MOE = NOAEL (4 mg/kg/day) ÷ Dermal Dose + Inhalation Dose **OR** Total MOE = 1 ÷ (1/Dermal MOE + 1/Inhalation MOE).

Post-Application Activities After Drench or Spray Treatments:

Table A.3.3. Occupational Post-Application Non-Cancer Dermal Exposure and Risk Estimates for Ethoxyquin.									
Crop/Site	**Activities**	**Max App. Rate (% ai in solution)[1]**	**Dermal Unit Exposure (µg/% ai)[2]**	**Inhalation Unit Exposure[2]**	**Dermal Dose (mg/kg/day)[3]**	**Dermal MOE[4] (LOC = 100)**	**Inhalation Dose (mg/kg/day)[5]**	**Inhalation MOE (LOC = 100)[6]**	**Total MOE (LOC = 100)[7]**
			SL/G	**No-R**	**SL/G**	**No-R**	**SL/G**		
Post-Harvest Pears	Sorter	0.006	10,500	6,720	0.00006	63,000	0.0005	7,900	7,100
	Packer		9,500	6,720	0.000057	70,000	0.0005	7,900	7,100

1. Maximum application rate based on representative label (Reg. No. 64864-58). 1:175 dilution ratio.
2. Based on Table 2 in ExpoSAC Policy/Guidance "Assessment of Occupational Exposure for Post-Harvest Commodity Pesticide Treatments" (M. Crowley, FEB-2018); Level of mitigation: SL/G = label required PPE for sorter/packers.
3. Dermal Dose (µg) = [UE (µg/% ai) * AR (% ai in solution) * AF(8%)] ÷ BW (80 kg)
4. Dermal MOE = Dermal POD (4 mg/kg/day) ÷ Dermal Dose.
5. Inhalation Dose (µg) = [UE (µg/% ai) * AR (% ai in solution) * AF] ÷ BW (80 kg)
6. Inhalation MOE = Inhalation POD (4 mg/kg/day) ÷ Inhalation Dose.
7. Total MOE = NOAEL (4 mg/kg/day) ÷ Dermal Dose + Inhalation Dose **OR** Total MOE = 1 ÷ (1/Dermal MOE + 1/Inhalation MOE).

Table A.3.4. Occupational Post-Application Non-Cancer Indirect Inhalation Exposure and Risk Estimates for Ethoxyquin.				
Crop/Site[1]	**Max App. Rate (% ai in solution)[1]**	**Inhalation Unit Exposure (µg/% ai)[2]**	**Inhalation Dose (mg/kg/day)[3]**	**MOE[4] (LOC = 1000)**
		NR	**NR**	**NR**
Pears	0.006	307	0.000023	170,000

1. Maximum application rate based on representative label (Reg. No. 64864-58). 1:175 dilution ratio.
2. Based on Table 4 in ExpoSAC Policy/Guidance "Assessment of Occupational Exposure for Post-Harvest Commodity Pesticide Treatments" (M. Crowley, FEB-2018); Level of mitigation: NR = no respirator.
3. Inhalation Dose (µg) = [UE (µg/% ai) * AR (% ai in solution) * AF] ÷ BW (80 kg)
4. Inhalation MOE = Inhalation POD (4 mg/kg/day) ÷ Inhalation Dose.

All tables are based on the most up-to-date information available at the time of the HASPOC meeting and are subject to change.